Role of PIN1 in human pathology: Cellular regulation, pathogenesis and therapeutic implications (Review)

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Abstract. Peptidyl-prolyl isomerase NIMA-interacting 1 (PIN1) plays a crucial regulatory role in cells, and it is the only enzyme capable of selectively binding to phosphorylated proline-directed serine/threonine (pSer/Thr-Pro) residues in target proteins and catalyzing their isomerization. The change in the conformational status of the protein, transitioning between *cis* and *trans*, affects its three-dimensional structure and, therefore, alters its function and stability. In this manner, PIN1 plays a role in the development of several human pathologies by regulating essential proteins. In cancer, the enzymatic activity of PIN1 induces conformational changes in essential proteins, promoting oncogenic processes and fostering aggressive tumor characteristics and resistance to chemotherapies. Moreover, the effects of PIN1 on viral infections are notable, as it interacts with viral proteins, enhancing their replication and infection mechanisms. In addition, PIN1 participates in autoimmune, cardiovascular, metabolic, neurodegenerative diseases and osteoporosis. These diverse functions render PIN1 as an attractive therapeutic target, leading to the development of PIN1 inhibitors. The critical role of PIN1 in human pathology is further underscored by its relevance to various diseases, rendering it a potential nexus for novel interventions in human pathologies.

Contents

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1. Introduction

Proline (Pro) is the only non-synthetic amino acid able to adopt *cis* or *trans* conformations. The process of transitioning between these conformations is known as isomerization. This process can be catalyzed by a group of proteins termed peptidyl-prolyl isomerases (PPIases) enzymes. Thus far, the only enzyme capable of recognizing and catalyzing the *cis-trans* isomerization of Pro in phosphorylated Ser/Thr-Pro motifs (p-Ser/Thr-Pro) is the peptidyl-prolyl *cis-trans* isomerase 1 interacting with NIMA (PIN1) (1) (Fig. 1A). The Ser/Thr-Pro motifs are one of the most crucial phosphorylation domains present in proteins (2). The alteration in the *cis-trans* conformation of the Pro within these domains, modulated by PIN1, emerges as another pivotal aspect in orchestrating intracellular signaling pathways (3).

PIN1 is composed of two domains: The 'WW' domain, responsible for the recognition and binding of PIN1 to the p-Ser/Thr-Pro motifs of its target proteins, and the PPIase, which provides PIN1 with its isomerase catalytic activity (4) (Fig. 1B). PIN1 can regulate and modify the destiny of numerous proteins through these two properties, affecting various signaling pathways and participating in numerous cellular processes. Such actions are achieved by influencing target proteins via diverse mechanisms, such as promoting activation or inhibition, altering cellular localization, affecting stability, and modifying interactions with other proteins (5).

This capacity of PIN1 to engage in a broad spectrum of cellular processes is accompanied by rigorous regulation. Under normal physiological conditions, PIN1 is tightly regulated at the transcriptional, post-transcriptional and post-translational levels (6-11). This regulatory framework ensures precise control over its activity and allows PIN1 to

orchestrate intricate protein modifications, thus contributing to the complex network of cellular signaling and responses.

The expression of PIN1 under normal physiological conditions is induced during neuronal differentiation. Generally, the expression level of this enzyme is directly associated with the replicative potential present in normal cells and gradually decreases with aging (12,13). Conversely, when some of the mechanisms that regulate PIN1 are disrupted, the deregulation of PIN1 can give rise to a range of pathologies. The present review aimed to systematically outline the diverse information on the dysregulation of PIN1 activity associated with various disorders, as enlisted in Fig. 2. By presenting a comprehensive synthesis of the currently available knowledge, the present review aimed to shed light on the multifaceted roles of PIN1 and its potential implications in disease mechanisms.

2. Metabolic diseases

Metabolic diseases (MetS) represent a constellation of related metabolic disturbances, such as insulin resistance, atherogenic dyslipidemia, central adiposity and high blood pressure. The pathogenesis of MetS involves various genetic and acquired factors related to insulin resistance and chronic systemic inflammation. If left unaddressed, MetS are strongly linked to a heightened susceptibility to developing diabetes and cardiovascular disorders. Together, MetS are currently known as metabolic syndrome (14).

Disordered insulin signaling is associated with various metabolic conditions, such as adiposity, non-alcoholic steatohepatitis (NASH), and type 2 diabetes (15). In this context, a number of researchers describe PIN1 as a vital regulator in insulin signaling. In the study by Nakatsu *et al* (16), it was demonstrated that PIN1 fosters insulin secretion in islet β-cells by heightening salt-inducible kinase 2 activity. Indeed, PIN1 encourages cellular proliferation and transformation by modulating activator protein-1 (AP-1) and ERK1/2 activation induced by insulin through interactions with p70S6K (16). Moreover, previous research has shown that PIN1 positively regulates signaling by promoting insulin receptor substrate 1 phosphorylation, increasing protein stability and the levels of acetyl-CoA carboxylase 1 and fatty acid synthase, and repressing AMPK activity in NASH (17). While the involvement of PIN1 in these metabolic disorders is partially due to its control of insulin signaling, it also interacts with or regulates key molecules relevant to other processes (Table I). For instance, in adipogenesis, PIN1 has been reported to function as an enhancer of adipocyte differentiation by regulating the function of PPARγ (18).

Additionally, it is involved in the function of adipocytes through its association with PR/SET domain 16 and patatin like phospholipase domain containing 2 (19). A recent study suggested that an increase in the expression of PIN1 in liver cells contributes to lipid accumulation in NASH (20). All these data lead to a better understanding of the role of PIN1 in MetS and its potential use as a therapeutic target.

3. Osteoporosis

Osteoporosis is a global disease associated in particular with advancing age, and it occurs when there is a loss of bone mineral density, leading to an increased predisposition to fragility fractures (21).

A keystone process that outlines this disease is the balance between osteoblasts and osteoclasts, which manage bone restoration and breakdown, respectively (22). In this regard, PIN1 is a key regulator of numerous pathways involved in osteoblast and osteoclast cell signaling. A clear indication is that PIN1-deficient mice exhibit osteoporosis-like characteristics with a low bone mass and density (23). In-depth studies reveal that PIN1 promotes osteoblast function and bone formation by enhancing bone morphogenetic protein signaling and associating with Runx2, a critical factor for osteoblast differentiation (24-26). By binding to Runx2 and Osterix, another essential factor for osteoblast differentiation, PIN1 boosts their transcriptional activity, thereby enhancing osteogenesis (27).

Conversely, PIN1 is a negative regulator of osteoclast fusion, leading to the accumulation of dense bone and promoting osteoporosis by reducing the activity of the dendritic cell-specific transmembrane protein, a key fusion-mediating molecule in osteoclastogenesis (23,28). In addition, several studies denote that genetics and regulatory factors regulate osteoporosis through multiple pathways, including Wnt, Notch and the MAPK signaling pathways (29-32). Furthermore, as reported by Xu *et al* (22), the cytokine network plays a crucial role in bone resorption and formation. Considering the participation of PIN1 in regulating a broad range of these signaling pathways (Table I), the role of this protein in a balance between osteoclasts and osteoblasts could be of utmost importance. Overall, further investigations are required to reveal the potential utility of PIN1 stabilizers, inhibitors, or activators for the treatment of osteoporosis.

4. Cardiovascular diseases

Cardiovascular diseases (CVDs) are a global disease, mainly related to an increasing age (21), involving a spectrum of pathological conditions. Atherosclerosis (AS), which underlies the majority of CVDs, is a persistent ailment that represents the primary cause of coronary heart disease, cerebral infarction and peripheral vascular disease (33).

The development of early-stage AS is primarily due to endothelial dysfunction. To maintain a healthy blood pressure and prevent AS, endothelial nitric oxide (NO) synthase (eNOS) plays a key role by producing NO, a vasodilator and a molecule that protects the vasculature (34). In this manner, PIN1 has been reported to function as a conformational switch in the modulation of the bioavailability of NO (35). Kennard *et al* (36) demonstrated that PIN1 regulated bovine eNOS activity by interacting with residues Ser116-Pro117 in a phosphorylation-dependent manner. Additionally, PIN1 has been identified as a crucial driver of vascular cell proliferation, apoptosis and inflammation, all implicated in various vascular diseases, such as AS, hypertension and cardiac hypertrophy (25,37).

Nonetheless, PIN1 regulates NO release by interacting with other intracellular factors involved in vascular homeostasis, such as vascular endothelial growth factor (VEGF) and transforming growth factor β (TGF-β) (35). TGF-β is a crucial mediator of endothelial-to-mesenchymal transition, a critical driver of vascular inflammation and AS (38). Despite the broad array of cellular activities, the TGF-β signaling route oversees,

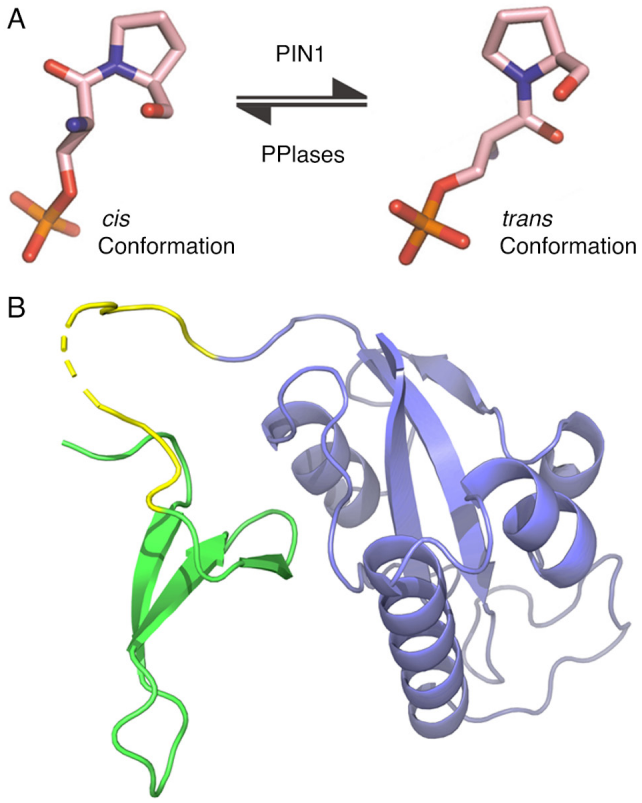

Figure 1. PIN1 function and structure. (A) PIN1 is the only PPiase that catalyzes the *cis-trans* isomerization of Pro in phosphorylated Ser/Thr-Pro motifs. (B) The main domains of PIN1: Green, the WW domain; blue, the PPiase domain; yellow, the intrinsic disorder loop. PIN1, peptidyl-prolyl isomerase NIMA-interacting 1; PPiase, peptidyl-prolyl isomerase; Pro, proline.

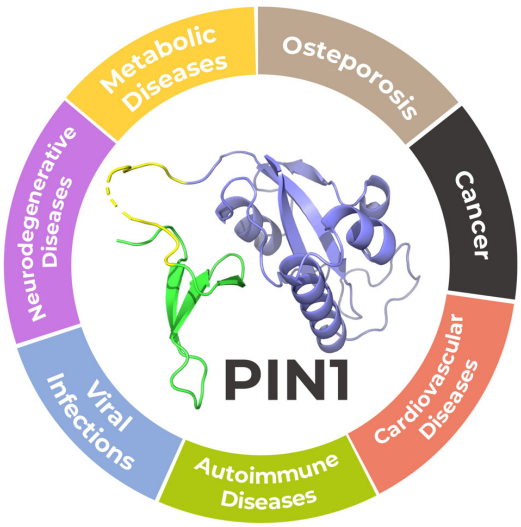

Figure 2. Summary of the multiple diseases associated with PIN1 dysregulation. PIN1, peptidyl-prolyl isomerase NIMA-interacting 1.

the mechanism is relatively straightforward. TGF-β family ligands attach to a type II receptor, leading to the recruitment and phosphorylation of a type I receptor. This type I receptor subsequently phosphorylates receptor-governed SMADs. Therefore, members of the SMAD family gather in the cell nucleus, functioning as gene regulators and aiding in the oversight of target gene output (39). Studies have demonstrated that PIN1 accelerates the degradation of SMAD2/3 ubiquitin proteasome brought about by the E3 ubiquitin-protein ligase Smurf2 and impedes TGF-β signal transduction, thereby effectively preventing the onset of AS (35). Furthermore, Kurakula *et al* (25) reported that the inhibition of PIN1 decreased TGF-β/SMAD2/3 signaling in cultured microvascular endothelial cells, representing a novel therapeutic strategy with which to reverse the abnormal vascular remodeling in pulmonary hypertension.

In addition, PIN1 is related to the activation of the VEGF signaling pathway. This pathway has been described as a central regulator of eNOS function (40). Regarding this, PIN1 has been reported as a positive regulator of the transcriptional and protein levels of VEGF by activating hypoxia-inducible factor-α and AP-1, promoting endothelial dysfunction and hypertension (41,42).

Lastly, researchers have demonstrated a pivotal role for PIN1 as a signaling network regulator in cardiac hypertrophy. In the myocardial context, through AKT and MEK-ERK cascade regulation, PIN1 activity influences signaling pathways, finally determining the overall outcome of the heart when challenged by hypertrophic stimulation (43).

Several studies have demonstrated that PIN1 plays a critical role in multiple cellular processes that govern CVDs (Table I). However, further in-depth investigations are necessary to reveal the specific functions of PIN1.

5. Cancer

Oncological diseases are among the most extensively documented pathologies linked to PIN1 dysregulation. PIN1 levels are markedly elevated in the majority of tumors, and its high expression is negatively associated with clinical prognosis. As previously outlined, this upregulation of active PIN1 in tumor cells invariably results from disruptions of the transcription and post-translation modifications governing PIN1 (44). The transcriptional and post-translational regulation of PIN1 is perturbed by various mechanisms that increase its expression and/or hyperactivation in cancer. Notable mechanisms include PIN1 overexpression mediated by the aberrant activation of oncogenes, such as E2F and NOTCH1, or alterations in tumor suppressor genes, such as BCRA1 and p53 (44).

Beyond its clinical associations, PIN1 can bind to and modulate the fate of an extensive pool of proteins harboring p-Ser/Thr-Pro motifs. Thus, it has been reported that PIN1 enhances the expression and/or activation of >50 oncogenes, while inhibiting the expression and/or activation of >25 tumor suppressor genes (44) (Fig. 3). The intricate network of proteins and cellular signaling pathways with which PIN1 can interact substantiates its molecular rationale for involvement in all pivotal cellular processes associated with tumorigenesis and progression, as previously described by Hanahan and Weinberg (45), such as sustained proliferative signaling, the evasion of growth suppressors, immune system evasion, replicative immortality, inflammation, invasion, angiogenesis, genomic instability, resistance to cell death and the dysregulation of cellular metabolism (46). This compilation of processes, collectively known as cancer hallmarks, expanded in 2022 to incorporate epigenetic reprogramming, senescent cell formation, phenotypic plasticity

Table I. PIN1-related processes involved in osteoporosis, metabolic and cardiovascular diseases.

Metabolic diseases (Refs.)	Osteoporosis (Refs.)	Cardiovascular diseases (Refs.)
Insulin signaling (16,17)	Osteoclast cell signaling and fusion (23,28)	Bioavility and release of nitric oxide (35,36)
Adipogenesis (18,19)	Osteoblast differentiation (24-26)	Vascular homeostasis (35,41,42)
Lipid accumulation (20)	Bone resorption and osteogenesis (22,27)	Apoptosis and inflammation (25,37,43)

PIN1, peptidyl-prolyl isomerase NIMA-interacting 1.

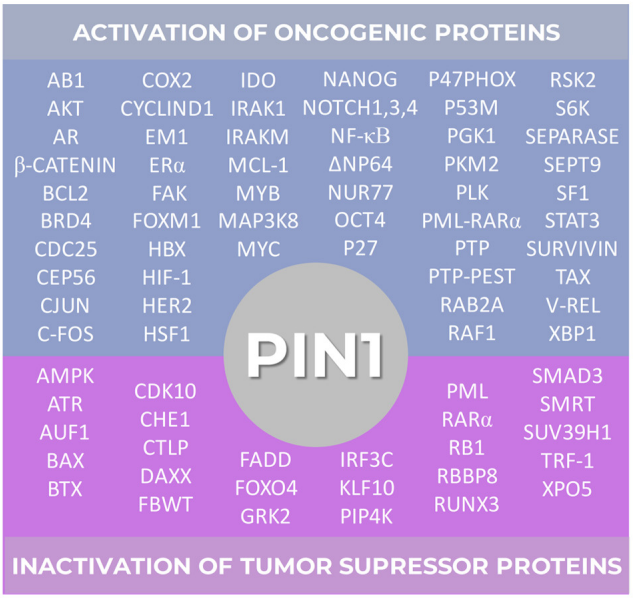

Figure 3. PIN1 is a key regulator in cancer signaling. Blue area: PIN1 promotes the activation of several oncogenic pathways. Purple area: PIN1 is involved in inhibiting multiple tumor suppressor signals. PIN1, peptidyl-prolyl isomerase NIMA-interacting 1.

and polymorphic microbiomes (47). There is suggestive evidence pointing towards the involvement of PIN1 mainly in two of these processes, as research has indicated its role in fostering cells with a stem-like phenotype and in regulating epigenetic modifications (48,49).

In this manner, this elucidates why PIN1 is upregulated in various types of human cancer, such as breast (50), prostate (51), lung (52), ovarian (53), gastric (54), esophageal (55), colorectal (56), cervical (57), melanoma (58) and brain tumors (59), which exhibit a heightened expression or activation of PIN1 in comparison to their corresponding normal tissues.

By contrast, single nucleotide polymorphisms in the promoter region of the PIN1 gene that reduce its expression exhibit a decrease in the susceptibility to developing multiple types of tumors (60). Additionally, PIN1 knockout mice exhibited resistance to oncogenesis, even following overexpression of specific oncogenes, such as HER2 and HRAS (61) or upon the mutation or deletion of the tumor suppressor gene TP53 (62,63).

6. Autoimmune diseases

Systemic lupus erythematosus (SLE). SLE is a systemic, debilitating autoimmune disease with a variety of clinical manifestations affecting multiple organs in the body (64). The Toll-like receptor 7 (TLR-7)/TLR-9/interleukin (IL)-1 receptor-associated kinase 1 (IRAK-1)/interferon regulatory factor 7 (IRF-7) pathway plays a key role in the development and progression of SLE (65-67). Furthermore, it has been observed that PIN1 activity is upregulated upon the activation of TLR7 or TLR9 and interacts with IRAK1 in primary dendritic cells. This interaction is crucial for IRAK1 activation and downstream signaling, including the activation of IRF7 and the induction of type I interferons. Indeed, PIN1 deficiency impairs the nuclear translocation of IRF7, thereby hampering TLR-mediated interferon-dependent immune responses (68). In this context, it has been demonstrated that PIN1 inhibition reduces SLE manifestations and improves overall survival in lupus-prone animal models (69).

In addition, IL-6, a pro-inflammatory cytokine produced by various cell types, has emerged as a crucial regulator in SLE. IL-6 affects the function of different cell types, including T- and B-cells, macrophages and neutrophils by promoting cell activation and differentiation, leading to systemic autoimmunity and subsequent inflammatory responses (70). Multiple studies have revealed elevated IL-6 serum levels in patients with SLE (71). In particular, the IL-6 pathway is suspected to play an essential role in B-cell hyperactivity and immunopathology in human SLE, and may directly mediate tissue damage. Thus, the blockade of IL-6 has been shown to improve the SLE phenotype in various models (72). Actually, IL-6 signaling is driven by the IL-6 receptor and the signal transducer and activator of transcription 3 (STAT3). It has been reported that PIN1 plays a critical role in inducing IL-6 expression in SLE by interacting with STAT3, promoting its phosphorylation at Ser727, and enhancing its transcriptional activity (73) (Fig. 4). Although further research is required to fully elucidate the underlying mechanisms and potential clinical applications, PIN1 inhibition emerges as a promising novel therapeutic strategy for patients with SLE (Fig. 4).

Rheumatoid arthritis (RA). RA is a complex autoimmune disorder characterized by chronic joint inflammation, the destruction of cartilage and bone, abnormal synovial cell proliferation, and the formation of an aggressive tumor-like structure termed pannus (74). Fibroblast-like synoviocyte samples from patients with RA have been observed to exhibit a neoplastic phenotype due to the activation of the NF-κB pathway (75). In addition, NF-κB, a critical player in inflammation and immunity, is pivotal in producing matrix metalloproteinases (MMPs) (76). These enzymes contribute to the destructive nature of RA by participating in cartilage destruction (77,78).

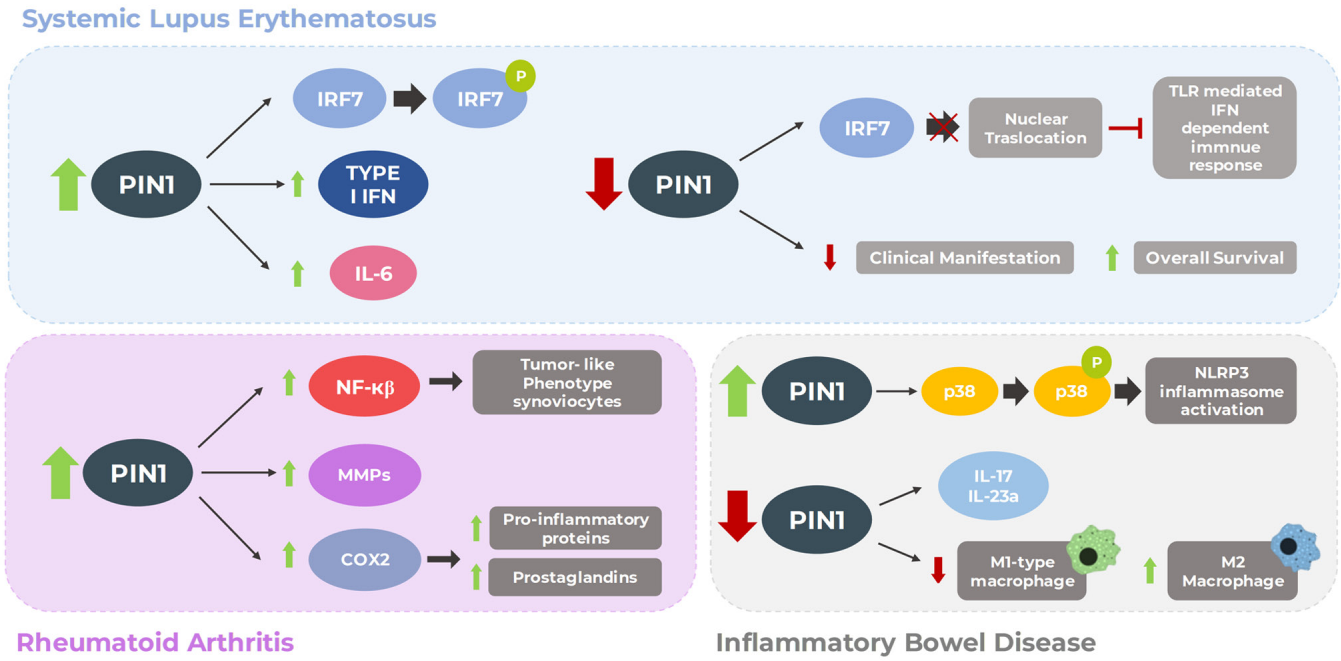

Figure 4. Main mechanisms affected by PIN1 in autoimmune diseases. PIN1 upregulation (green arrows) and downregulation (red arrows) are involved in key signaling pathways implicated in disease progression. PIN1, peptidyl-prolyl isomerase NIMA-interacting 1; IRF7, interferon regulatory factor 7; IFN, interferon; MMPs, matrix metalloproteinases; COX2, cyclooxygenase 2; IL, interleukin; TLR, Toll-like receptor; NLRP3, NOD-like receptor family pyrin domain-containing protein 3.

Notably, PIN1 has been reported to upregulate NF-κB activity, thereby promoting the tumor-like phenotype of RA synoviocytes. Indeed, an association has been found between the expression of MMPs, NF-κB subunits and PIN1 in the synovial tissue of patients with RA (75).

Moreover, the progression of RA is dictated by inflammatory mediators, such as prostaglandins (PGs) and pro-inflammatory cytokines, that orchestrate the immune response (79,80). Cyclooxygenase 2 (COX2) controls PG production. Notably, in a previous study, both COX2 and PIN1 expression levels were found to be increased in the ankle tissue of mice with RA following induction with type II collagen (81). The overexpression of PIN1 led to the increased expression of COX2. Moreover, it was shown that during the progression of RA, PIN1 induction stimulated the expression of pro-inflammatory proteins, such as iNOS, TNF-α and IL-1β by activating NF-κB, CREB and the C/EBP pathways. Consistently, PIN1 inhibition significantly reduced RA progression and COX2 expression in ankle tissues (81) (Fig. 4). Given the complex interplay of PIN1 and its impact on RA, further research is essential to uncover its potential role as a therapeutic target for the treatment of RA.

Inflammatory bowel diseases (IBDs): Crohn's disease and ulcerative colitis (UC). IBDs are chronic relapsing disorders encompassing Crohn's disease and UC affecting the colon and small intestine. Symptoms range from chronic diarrhea and abdominal pain to inflammation and epithelial injury involving the gastrointestinal tract. Although the etiology of IBDs remains unknown, it has been proposed that intestinal mucosa damage occurs due to the dysregulated abnormal immune response against the microorganisms of the intestinal flora (82).

Matsunaga *et al* (83) suggested the contribution of PIN1 to the development and severity of IBDs. Indeed, its expression was shown to be markedly enhanced in the colons of model mice with dextran sodium sulfate (DSS)-induced UC. A PIN1 knockout mouse model consistently exhibited significantly reduced DSS-induced colitis symptoms and colon tissue damage. In the colons of PIN1 knockout mice, its inhibition decreased M1-type macrophages, known for their pro-inflammatory cytokine expression (83). Conversely, M2 macrophages, a producer of anti-inflammatory cytokines, exhibited an increased percentage. Furthermore, PIN1 inhibition was associated with the downregulation of IL-17 and IL-23a expression, cytokines implicated in IBD development (83).

Of note, the NOD-like receptor family pyrin domain-containing protein 3 (NLRP3) is exclusively expressed in several inflammatory and autoimmune diseases. This innate immune receptor triggers the inflammasome complex assembly, which has been reported to be associated with various inflammation- and immune-related diseases that are a key factor in the pathogenesis and progression of UC and Crohn's disease. Indeed, the overexpression, aberrant activation, polymorphism and gain-of-function mutation of the NLRP3 inflammasome contribute to IBD pathogenesis (84). Additionally, it has been suggested that PIN1 promotes NLRP3 inflammasome activation through the phosphorylation of the p38 MAPK signaling pathway in macrophages (85) (Fig. 4). A comprehensive understanding of the role of PIN1 in activating NLRP3 necessitates further research on IBDs.

Nonetheless, additional exploration is necessary to unveil its potential as a therapeutic focal point for addressing RA.

7. Viral infections

Viruses are prevalent infectious agents leading to contagious diseases. Upon a viral attack, the host triggers its innate

immune response to combat or eliminate the infection (86). However, specific proteins within the host assist the virus in minimizing the host's resistance or facilitating the viral infectivity process. In this framework, PIN1 has been identified as one of these proteins that share a strong association with viral infections (Table II) (87).

Hepatitis C virus (HCV). HCV is the primary infectious agent of acute and chronic hepatitis, which can eventually lead to permanent liver damage and hepatocellular carcinoma (HCC). HCV, a sheathed RNA virus, has its reproduction reliant primarily on the host cell cycle and requires the involvement of host proteins (88). In particular, PIN1 is a cellular factor required for HCV replication, and it may enhance the viral infection principally due to its interaction with both the NS5A and NS5B HCV proteins. Specifically, PIN1 interacts with the p-Ser/Thr-Pro motifs of NS5A and NS5B, stabilizing them. Notably, Lim *et al* (89) demonstrated that increased levels of PIN1 were associated with higher levels of intracellular HCV RNA and these viral proteins.

By contrast, when PIN1 is inhibited, it prevents the propagation of HCV by disrupting the interaction between PIN1 and these proteins. Furthermore, NS5B can increase the expression of PIN1, thus promoting its spread (89). Therefore, PIN1 may be exploited as a host target to impair HCV reproduction and infection, emerging as a potential target for antiviral therapies.

Hepatitis B virus (HBV). HBV is a virus that can lead to chronic hepatitis B, causing cirrhosis, liver failure and HCC. Its genome in the viral capsid is relaxed circular DNA, and when it enters the hepatocyte nucleus, it is converted to covalently closed circular DNA (cccDNA). The transcription of the viral cccDNA is modulated by the HBV-encoded protein, HBx (90). Of note, there is evidence to indicate that PIN1 is overexpressed in HBV-related HCC and that HBx comprises two p-Ser-Pro motifs that can serve as potential targets for PIN1. Actually, PIN1 binds to HBx through its Ser41-Pro motif, enhancing its stability and transactivation, and thereby promoting hepatocarcinogenesis (91,92).

HBx-activated AKT and ERKs also phosphorylate and inactivate glycogen synthase kinase-3β (GSK-3β), leading to the stabilization of β-catenin and cyclin D1 gene transcription, and promoting the development of HCC (93). The overexpression of PIN1 not only elevates the expression of cyclin D1, but also encourages the intracellular buildup of β-catenin in the Wnt/β-catenin signaling pathway. These two signaling pathways can trigger the expression of oncogenes and encourage the occurrence of HCC in HBV infection (94).

In addition, HBV is formed with a core particle composed of multiple HBV core protein (HBc) molecules. Notably, PIN1 has been observed to interact with HBc at the p-Thr160-Pro and p-Ser162-Pro motifs and promote its stability to sustain efficient HBV replication (95). Conversely, Kwon *et al* (96) recently reported that PIN1 interacts with HBV core particles, but not HBc dimer or monomer. Moreover, they posited PIN1 as a positive regulator of HBV propagation and that the interaction between PIN1 and the core particle may be involved in HBV-associated hepatocarcinogenesis., supported by the observation that PIN1 overexpression enhances, while its knockdown reduces it (96).

Epstein-Barr virus (EBV). EBV, a highly prevalent virus, infects 95% of individuals worldwide at some point. While often asymptomatic, some develop infectious mononucleosis (97). Additionally, an association exists between EBV infection and Burkitt lymphoma and T-cell malignancies (98). Considering the main processes in EBV infection, one of the interesting aspects to analyze is the role of PIN1 in replication. By performing PIN1 knockdown, Narita *et al* (99) reported that PIN1 promoted viral DNA replication through its interaction with the p-Thr178-Pro motif in the EBV DNA polymerase subunit.

In addition, EBV infection is closely related to nasopharyngeal carcinoma (NPC). The majority of cases of NPC exhibit a distinctive feature: They are nonkeratinizing carcinomas associated with EBV infection (100). In this context, previous studies have demonstrated that PIN1 is overexpressed in all EBV-associated NPC cells, contributing to the growth and aggressiveness of cancer (101,102).

Human T-cell leukemia virus type 1. Adult T-cell leukemia/lymphoma is an uncommon malignancy caused by human T-cell lymphotropic virus type I (HTLV-1) (103). The HTLV-1 encodes for an oncoprotein known as Tax and this plays a crucial role in viral gene expression. This protein influences NF-κB signaling pathways, perturbing the normal cell cycle, interfering with apoptosis and prompting genomic instability (104). Tax interacts with a number of human cellular proteins to regulate viral gene expression and foster the pathogenic activation of signaling pathways, such as NF-κB (105). Notably, PIN1 is highly expressed in adult T-cell leukemia cells expressing Tax protein (106). By triggering the E2F/RB pathway, TAX enhances the expression of PIN1. Furthermore, PIN1 binds to Tax when phosphorylated in the p-Ser160-Pro motif in the presence of mitotic kinases (106). Due to PIN1 regulation, phosphorylated Tax interacts with IKKγ to enhance NF-κB activation, promoting cancer progression (107). Furthermore, PIN1 can determine Tax stability by regulating its ubiquitination and lysosomal degradation (106).

High-risk human papillomavirus (HR-HPV). HR-HPV can cause cancers of the cervix, vagina, vulva, penis, anus and the back of the throat, including the base of the tongue and tonsils (oropharynx), in both males and females (108). The most frequent type of cancer caused by HR-HPV is cervical cancer, with an annual incidence of >500,000 new cases worldwide (109). Of note, ~14 HR-HPV types are responsible for the majority of cervical cancers, mainly HPV16 and HPV18. The viral protein E2 is a determinant factor that manages viral replication and transcription, and it is employed as an early indicator of HPV infection (110). Notably, HPV-infected cervical lesions exhibit an elevated level of PIN1 (44). The increased expression of PIN1 in cervical cancer can enhance the nuclear sequestration of NF-κB (46) and stimulate the transactivation of STAT3, thereby advancing the onset of cancer (48,111). Even a slight, yet significant increase in PIN1 expression has been observed in E2-transfected 293 cells; E2 has been reported to amplify the functionality of PIN1. This evidence suggests that PIN1 activity is addressed by the E2 modulation of the transcription factors, NF-κB and STAT3, driving thus cancer progression (112).

Table II. Main PIN1-regulated targets and their effects on viral infection.

	Target	Effect	(Refs.)
Hepatitis C virus	p-Ser/Thr-Pro motifs of NS5A and NS5B.	Enhancing viral replication and propagation	(89)
Hepatitis B virus	p-Ser41-Pro motif of HBx.	Promoting development of HCC	(91,92)
Epstein-Barr virus	p-Thr78-Pro motif of BALF5.	Enhancing viral DNA replication	(99)
Human T-cell leukemia virus type I	p-Ser160-Pro motif of Tax.	NF-κB activation, promoting cancer progression.	(106)
High-risk human papillomavirus	NF-κB and STAT3.	Promoting development of cancer.	(48,111)
Human immunodeficiency virus	p-Ser16-Pro motif of HIV capsid protein. Host protein A3G. p-Ser57-Pro motif of HIV integrase.	Discarding capside proteins. Enhancing reverse transcription of HIV genome Promoting HIV cDNA integration.	(117,118) (116) (119)
Severe acute respiratory syndrome coronavirus-2	p-Ser79-Pro motif of the N protein.	Not yet described.	

PIN1, peptidyl-prolyl isomerase NIMA-interacting 1; HCC, hepatocellular carcinoma.

Human immunodeficiency virus (HIV). HIV is a lentivirus that targets predominantly $CD4^+$ T-lymphocytes and macrophages. Since these T-cells are the regulators of the adaptive immune system, their depletion effectively weakens the immune system, leading to acquired immune deficiency syndrome (AIDS) (113). Several host factors have been shown to play an essential role in the HIV life cycle (114). PIN1 is one of these factors, enhancing HIV infection by being involved in three vital stages of the HIV replication cycle: Cell entry, reverse transcription and host genome integration (115,116). The HIV core depends on PIN1 to discard capsid proteins. PIN1 links to the p-Ser16-Pro17 motif of the HIV capsid protein, reorganizing its structure and removing the capsid from the HIV core (117,118). Furthermore, PIN1 eases the reverse transcription of the HIV genome. The host protein A3G can be packaged into viral particles and induces alterations in DNA during HIV genome reverse transcription. HIV-1 expresses Vif protein to resist the activity of A3G by mediating A3G degradation. Regarding this, PIN1 diminishes A3G expression and prevents A3G from entering HIV particles (87,119). Finally, Saleh *et al* (116) reported that PIN1 bound to the HIV integrase through its pSer57-Pro motif, thus stabilizing and promoting integrase activity. Consequently, PIN1 improved the insertion of the HIV cDNA into the host genome (116).

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The unprecedented outbreak of novel coronavirus disease 2019 (COVID-19) emerged as a worldwide pandemic, causing profound effects on societies across the globe. SARS-CoV-2 is a highly transmissible and pathogenic enveloped, plus-stranded RNA virus with a single-stranded RNA genome (120). Recently, it was established that PIN1 plays a crucial role as a cellular component essential for the propagation of SARS-CoV-2. Yamamotoya *et al* (121), by using the siRNA-mediated silencing of PIN1 expression, significantly reduced the proliferation of SARS-CoV-2 in VeroE6/TMPRSS2 cells. Several recently developed PIN1 inhibitors exhibited potent suppressive effects on SARS-CoV-2 proliferation, as evidenced by reductions in both viral mRNA and protein synthesis, leading to the mitigation of the cytopathic effect on VeroE6/TMPRSS2 cells (121). Furthermore, Ino *et al* (122) reported that PIN1 bound precisely to the p-Ser79-Pro motif of the SARS-CoV-2 N protein. However, further in-depth investigations are warranted to elucidate the effects of this interaction on the viral progression. One particular compound, H-77, has demonstrated the ability to block SARS-CoV-2 proliferation with an EC50 <5 μM, regardless of whether it is administered to the culture medium before or following SARS-CoV-2 infection (121). The inhibition of viral N protein mRNA synthesis by H-77 suggests that the underlying molecular mechanism responsible for SARS-CoV-2 suppression likely involves viral gene transcription or earlier stages of infection (121). Another PIN1 inhibitor, all-trans retinoic acid, known to activate the retinoic acid receptor while inhibiting PIN1 activity, also reduced SARS-CoV-2 proliferation. These findings collectively suggest that PIN1 inhibitors are promising therapeutic agents for combatting COVID-19 (121).

8. Neurodegenerative diseases

Apart from its role in bodily functions, an increasing amount of data point to the vital participation of PIN1 in neurodegenerative disorders, such as Alzheimer's disease (AD), Parkinson's disease (PD), frontotemporal dementia (FTD), Huntington's disease (HD) and amyotrophic lateral sclerosis (ALS). It exhibits a broad spectrum of impacts in these conditions, from safeguarding nerve cells to causing them harm (Fig. 5).

PD. PD is recognized as the most common neurodegenerative movement disorder. It affects multiple systems, entailing a variety of motor and non-motor symptoms. Pathologically, Lewy bodies (LBs) are the characteristic protein conglomerates in tissues of PD, spanning from the gastrointestinal tract to the neocortex (123). LBs are primarily composed of

α-synuclein (124), which is an unstructured protein in its natural state, but can be induced to form an indissoluble α-synuclein cluster in the pathological condition (125). Synphilin-1 is a protein that can interact with α-synuclein, leading to the formation of debris inclusion bodies in the cytoplasm; this interaction plays a central role in creating LBs (126). Due to the absence of a p-Ser/Thr-Pro pattern in α-synuclein, PIN1 does not bind directly to free molecules, but influences α-synuclein through indirect mechanisms (127). When synphilin-1 is phosphorylated, PIN1 can bind through Ser211-Pro and Ser215-Pro patterns, thus indirectly interacting with α-synuclein. The increased expression of PIN1 can impede the degradation of α-synuclein, prolong its half-life, promote its insolubility and contribute to the formation of debris inclusion bodies (128). Hence, it can be speculated that inhibitors targeting PIN1 might alleviate the progression of PD.

AD. AD is a progressive neurodegenerative disorder primarily affecting cognitive functions, particularly memory, thinking and behavior. It is the most common cause of dementia among older adults (129). The disease is characterized by the abnormal accumulation of protein aggregates, including plaques and intracellular neurofibrillary tangles (NFTs). NFTs are clumps of microtubules formed due to the excessive phosphorylation of Tau protein (130). Extracellular plaques mainly consist of aggregates of amyloid-β-peptides resulting from the increased processing of amyloid precursor protein (APP) (131). In the neuronal cells of patients with AD, PIN1 expression is typically downregulated and demonstrates an inverse association with the degeneration of neuronal fibers. In addition, PIN1 facilitates the conformational conversion of GSK-3β-mediated phosphorylated Tau proteins from the dysfunctional *cis* form to the functional *trans* form, thus promoting the degradation of Tau proteins (132). Furthermore, PIN1 induces the phosphorylation of APP Thr668-Pro, transitioning it to *trans* isomer and redirecting APP processing towards non-amyloidogenic pathways (1). PIN1 can directly impede the activation of GSK-3β by binding to the phosphorylated Thr330-Pro motif and catalyzing its isomerization (133). There is evidence to suggest that a decrease in PIN1 expression in the brain generally increases susceptibility to AD and, on the other hand, its overexpression in mature neurons can protect against neurodegeneration caused by Tau hyperphosphorylation (134).

HD. HD is a progressive neurodegenerative disorder characterized by abnormal and repetitive expansions within exon 1 of the gene encoding CAG in the huntingtin protein (HTT), responsible for the degeneration of striatal neurons in the brain (135). The mutated huntingtin protein (mHTT) forms an intranuclear inclusion through misfolding and aggregation (136), which is harmful and it leads to glial proliferation of astrocytes and selective loss of striatal neurons (137). Additionally, it can induce the DNA damage response (DDR) in neurons (138), a significant pathological characteristic of HD. Research has discovered that p53 mediates this cytotoxicity in HD cells and transgenic animal models, and its inhibitors hinder this process (138). Conversely, when PIN1 is silenced, p53 binds to iASPP (a critical inhibitor oncoprotein of p53) regardless of mHTT expression, resulting in the failure to induce apoptosis and consequently preventing mHTT-related neurodegeneration (139). Furthermore, PIN1 is also implicated in DDR and the regulation of DNA double-strand break repair (140).

FTD. FTD is a clinical disorder associated with the neurodegeneration of the cortex of the frontal and temporal lobes, often in conjunction with the degeneration of subcortical brain areas. In consequence, behavior, executive function, or language are compromised. FTD is caused by genetic mutations, environmental factors and protein abnormalities (141). Recently, researchers have observed decreases in PIN1 levels across various forms of FTD. These observations have not only been observed in FTD cases with Tau pathology, such as FTD with Tau mutation, Pick disease and cortico-basal degeneration, but also in cases without Tau pathology, such as FTD with motor neuron-type inclusions and neuronal intermediate filament inclusion disease (134).

Additionally, in neurons sourced from the middle frontal gyrus, a shift of PIN1 from the nucleus to the cytoplasm has been identified in all FTD cases, as opposed to typical brains, which conversely exhibit a primary nuclear localization of PIN1 (142). Research has demonstrated that the anomalous detected translocation of the mitotic regulator PIN1 depends on the presence of p-Tau, along with the elevated quantity of other target phosphoproteins in neuronal cytoplasm, such as mitotic phospho-epitopes and cell cycle–associated proteins (143). A buildup of these proteins has been noted in diverse pathological contexts (e.g., AD, FTD, parkinsonism linked to chromosome 17, progressive supranuclear palsy and cortico-basal degeneration) and described as signs of the interrupted mitotic process causing cytoskeletal abnormalities and neuronal apoptosis (144). However, additional studies are required to determine whether PIN1 translocation to the cytoplasm represents an early event driving the neurodegenerative processes or if it emerges due to FTD.

ALS. ALS is a nerve-deteriorating disease affecting the upper and lower motor neurons, resulting in the paralysis of voluntary muscles, swallowing difficulties, speech impairment and respiratory collapse (145). Recently, Iridoy *et al* (146) demonstrated a notable downregulation in PIN1 expression in the spinal cord and non-motor cortex of a select group of patients with ALS, signifying PIN1 expression as a potential neurodegeneration indicator. Nonetheless, the existing understanding of the expression profile of PIN1 in ALS is exceedingly limited, as is its role in the pathophysiology of the disease. The literature suggests it may encourage the abnormal piling up of phosphorylated neurofilament proteins in the perikaryon, a significant characteristic of ALS and other nerve-deteriorating diseases. Consistently, PIN1 has been reported to link with phosphorylated neurofilament heavy chain (NF-H) in neurons and to co-locate in ALS-impacted spinal cord neuronal inclusions (147). In rat dorsal root ganglion cultures, exposed to excitotoxic stress to provoke the accumulation of phosphorylated NF-H within the cell body to imitate neurodegeneration, glutamate-induced harm has been shown to heighten phosphorylated NF-H in perikaryal accumulations that co-localized with PIN1 and induce neuronal apoptosis. These effects are mitigated through pharmacological intervention or siRNA-mediated reduction of PIN1

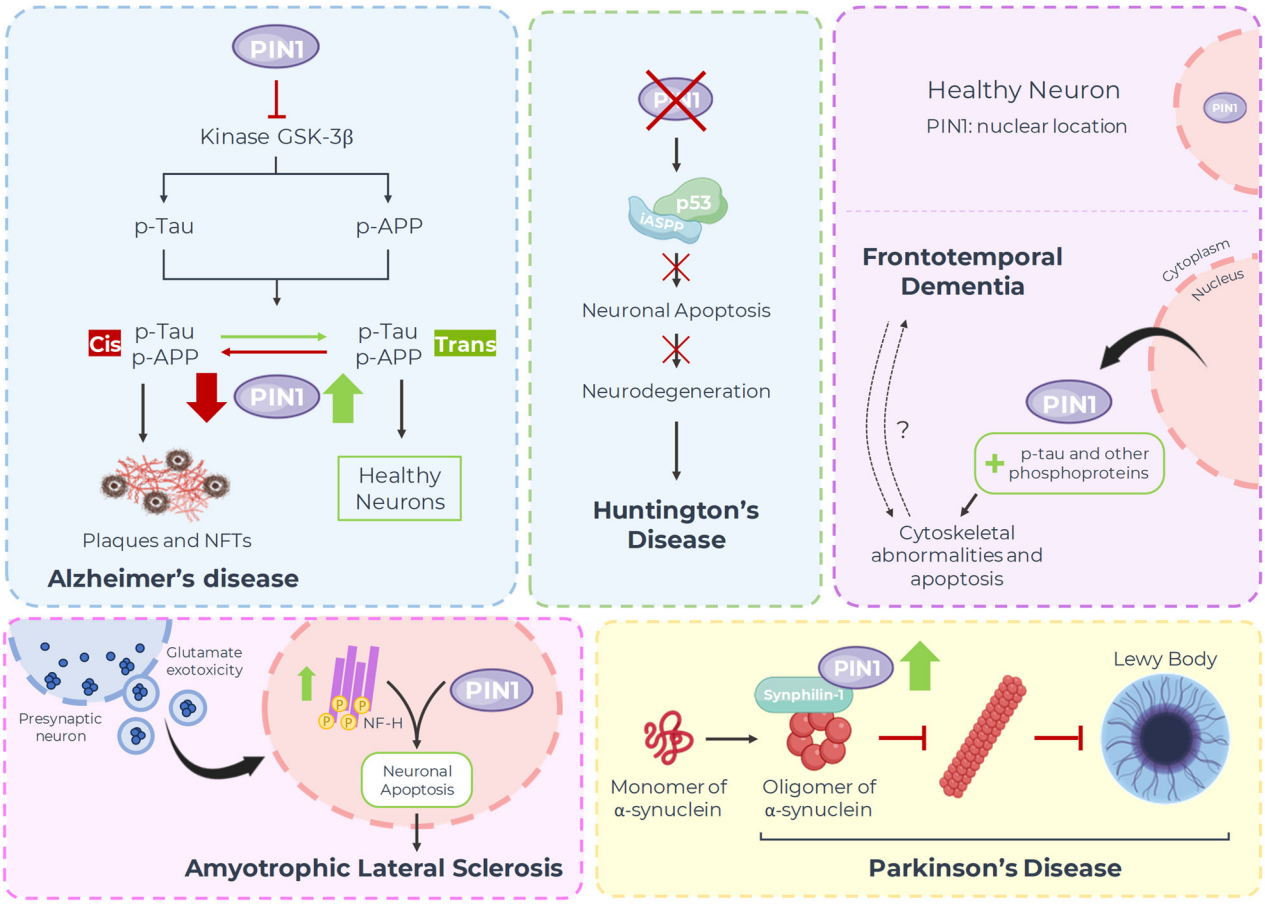

Figure 5. PIN1 deregulation in neurodegenerative disorders. The main cellular processes implicated in any particular disease are illustrated. PIN1, peptidyl-prolyl isomerase NIMA-interacting 1; GSK-3β, glycogen synthase kinase-3β; APP, amyloid precursor protein.

expression, implying that in the face of neurotoxic stress, PIN1 can potentially promote cell death by triggering the assembly of phosphorylated NF-H in the perikaryal (148).

9. PIN1 inhibitors

Given the involvement of PIN1 in a wide range of pathological conditions, pharmaceutical firms and several academic research teams have directed their efforts toward formulating novel strategies for PIN1 inhibition, aiming to exploit the therapeutic promise offered by these inhibitors.

Some natural compounds that have exhibited the ability to bind to PIN1 were identified in the past. Juglone, or 5-hydroxy-1,4-naphthoquinone, was the first of these to be described (149). This molecule, produced by the walnut tree, functions as an inactivator (not an inhibitor), forming Michael adducts with Cys113 of PIN1. The PIN1-juglone complex has a reduced stability within cells, and is ubiquitinated and rapidly degraded via the proteasome pathway, rendering it inappropriate for commercialization (149). Another natural compound that can bind to PIN1 is epigallocatechin-3-gallate (EGCG) (150). This compound is the main flavonoid in green tea and has been shown to exhibit antitumor activity. X-ray information obtained from the co-structures has indicted that EGCG can bind to both the WW and PPIase domains. However, subsequent analyses have indicated that its PIN1 inhibitory activity is due to binding to the WW domain (150).

The study of the complexes that these inhibitors form with PIN1 has provided critical information about the structural biology of this protein, its interactions and the identification of possible key amino acids for its function. The first developments of specific PIN1 inhibitors were based on the information provided by these natural compounds. However, a number of molecules with different chemical compositions have been developed over the past decades. These compounds can be broadly divided according to whether they bind to the PPIase or WW domains.

PPIase inhibitors. Since the PPI domain is the catalytic domain that provides PIN1 with its isomerase activity, it is not surprising that the vast majority of efforts to find a specific inhibitor of PIN1 have focused on this region of the protein. Below, the developments that were consider most relevant, grouped according to the chemical nature of the inhibitors are described.

Peptides. The primary strategy used to develop PIN1 inhibitors was based on peptide molecules. In 2005, Bayer *et al* (151) developed a library of synthetic peptides inhibiting PIN1 using the natural peptide pepticinamin E as the base structure. Thereafter, various developments of PIN1 peptide inhibitors emerged with different rational modifications to improve the binding capacity to this protein and, at the same time, problems caused by the nature of this type of molecule, such as its low-cell permeability and high degradation, highlighting

the development of modified cyclic peptides that substantially increase their stability and ability to cross cell membranes. These peptides were shown to exert an anti-proliferative effect *in vitro* on HeLa cells (152). It should be noted that although the translation of these peptides to PIN1 inhibitor drugs is extremely complex, all these efforts and research provided a large volume of information that allowed for the characterization of different mechanisms to inhibit the PPI domain, which were elegantly reviewed by He *et al* (153).

Small molecules. As regards the evaluation of small molecules derived from drug design based on the structure of PPI domain inhibitors, in 2009, Pfizer searched PIN1 inhibitors with a massive analysis of more than one million compounds. Although several candidate compounds were obtained, orthogonal assays for biological activity or co-crystallization were not performed (154).

In a recent study, Russo Spena *et al* (155) searched for PIN1 inhibitors using a library of 35,000 low-molecular-weight compounds through virtual screening based on docking, targeting the PPI domain. This strategy was complemented with molecular dynamics simulations to reduce the number of candidates. Among these, they identified a compound that demonstrated binding to PIN1, and simultaneously, this compound exhibited antiproliferative effects in four different ovarian cancer cell models. It is worth noting that treatments with the candidate compound also reduced signaling pathways associated with PIN1 (155).

Covalent inhibitors. Covalent inhibitors are a group of chemical compounds that establish permanent bonds with specific proteins, thereby modifying their function and regulation. These inhibitors are highly valued in research and drug development due to their exceptional selectivity and potency. However, they also present challenges in terms of design and the potential for unintended side-effects due to off target nonspecific irreversible binding.

The first PIN1 covalent inhibitor described after the natural compound Juglone was KPT-6566. This inhibitor obtained by mechanism-based screening can selectively inhibit PIN1 and target it for degradation by binding to the PPI domain. This interaction induces cell death in cancer cells *in vitro* and reduces the growth of lung metastasis *in vivo* (156).

In a recent study, Liu *et al* (157) screened using an in-house library of 2,000 electrophilic compounds. Following a series of structural optimizations, they successfully obtained a more potent compound named ZL-Pin13. The covalent binding of this compound with PIN1 was confirmed through crystallography. This compound exerted anti-proliferative effects in breast cancer cell models with IC50 values <3 μM. It also reduced the levels of proteins associated with PIN1, such as Cmyc, Mcl-1 and cyclin D1 (157).

WW inhibitors. The WW domain is essential, granting PIN1 the unique ability to specifically recognize and bind to pSer/Thr-Pro motifs of its target proteins (158). It is important to note that recent research has highlighted the critical importance of the WW site for the proper functioning of the PIN1 protein:

The PIN1 WW domain is phosphorylated on Ser16 both *in vitro* and *in vivo*. This phosphorylation regulates the ability of the WW domain to mediate Pin1 substrate interaction. Thus, Ser16 may be critical for regulating WW domain binding activity and Pin1 function (159).

On the other hand, it has been demonstrated that a mutant with the Trp34Ala mutation, which is a highly conserved amino acid in the WW domain of PIN1, experiences a 20-fold reduction in its binding affinity for substrates due to sustained inter-domain contact (160). Consequently, the catalytic pocket remains in a suboptimal conformation and exhibits diminished enzymatic activity (161).

Despite the crucial role of this domain, efforts to develop specific inhibitors targeting WW have been notably limited compared to those directed toward the catalytic PPI domain of PIN1. Nonetheless, it is considered that the flat and shallow interface of the WW domain does not provide a favorable starting point for the rational design of potent PIN1 inhibitors (153).

The most prominent example of an inhibitor designed for the WW domain of PIN1 is a semi-synthetic compound derived from the natural compound, acetyl-11-keto-β-boswellic acid. This inhibitor been shown to exert anti-proliferative and pro-apoptotic effects in prostate cancer cells, underscoring the therapeutic potential of targeting this domain (162).

In this regard, the authors' research team has achieved significant progress by embarking on the first *de novo* design of inhibitors explicitly tailored to bind to the PIN1 WW domain. The authors previously conducted structural analyses of Trp34 and its vicinity within the WW domain. Through this series of analyses, a novel allosteric region was identified within this domain, constituting a novel pharmacological pocket. By employing a combination of *in silico* virtual screening based on docking and *in vitro* biophysical assessments, four small molecules out of 450,000 compounds were successfully identified, that exhibited a high affinity for PIN1 (163).

Their distinctiveness compared to other PIN1 inhibitors lies in their exclusive and specific targeting of the WW region, in contrast to other inhibitors that interact with the conserved catalytic PPI domain of PIN1, a feature shared by other peptidyl prolyl isomerases. These efforts represent an essential step in expanding therapeutic options for addressing pathologies associated with the PIN1 protein and highlight the as-yet-unexplored potential of this domain as a therapeutic target.

10. Conclusions and future perspectives

In conclusion, the present review has contributed to a better understanding of the implications and potential functions of PIN1 in multiple ailments. The majority of pharmaceutical products developed to target PIN1 are focused on cancer therapy, considering its upregulation in cancerous tissues and its role in tumor progression. Conversely, there is a notable lack of research and application of PIN1 inhibitors and agonists in other pathologies, indicating the need for more comprehensive and more profound studies to unveil the therapeutic potential of PIN1 modulators. Several investigations strongly suggest that upstream regulatory signals and downstream targets of PIN1 establish an attractive field that has not yet been fully explored, which may provide new insight into the treatment of the multiple pathologies reviewed herein.

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Authors' contributions

JM wrote the 'Introduction', 'Cancer' and 'PIN1 inhibitors' Sections. RGA wrote the 'Cardiovascular diseases', 'Metabolic diseases' and 'Osteoporosis' sections. LB wrote the 'Autoimmune diseases' section. RNV wrote the 'Neurodegenerative diseases' section. MDPC and DLMG wrote the 'Viral infections' section. RGA and LB prepared the figures and tables. DEG and DLMG functioned as co-supervisors and were also involved in the writing of the sections. DEG conceived the study and, compiled and corrected the final version of the manuscript. All authors have read and approved the final manuscript. Data authentication is not applicable.

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Competing interests

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